REMARKS

Claims 21-40 are pending in the application. Claims 21, 22, 30, and 32-40 are withdrawn as being drawn to non-elected inventions. Applicants reserve the right to prosecute the non-elected claims in subsequent divisional applications. Claims 23-29 and 31 are currently being examined on the merits. The Examiner is respectfully reminded that claims 32-34, 39, and 40, directed to methods of using the claimed polynucleotides, are entitled to rejoinder upon allowance of a product claim per the Commissioner's Notice in the Official Gazette of March 26, 1996, entitled "Guidance on Treatment of Product and Process Claims in light of *In re Ochiai, In re Brouwer* and 35 U.S.C. § 103(b)" which sets forth the rules, upon allowance of a product claim, for rejoinder of process claims covering the same scope of products.

Objections to the claims:

Claims 23 and 24 are objected to as being dependent upon non-elected claims 21 and 22.

The Office Action dated March 25, 2003, stated that the DNA and protein may be searched and examined together if the claim set is drafted as in Example 17's format and if the DNA and protein are both free over the prior art. The Office Action dated March 25, 2003 stated that SEQ ID NO:1 was not free over the prior art, as reference polynucleotides AA779652 and AA447814 had identity over portions of polynucleotides encoding SEQ ID NO:1. Applicants respectfully note that the claims are directed to **SEQ ID NO:22/101**, not to SEQ ID NO:1 or polynucleotides encoding it. **No evidence has been presented in the current or previous Office Action that either SEQ ID NO:22 or SEQ ID NO:101 are not free of the prior art.** Thus Applicants believe that unity of invention should be applied since the claims are linked by a special technical feature (the sequence of SEQ ID NO:22, encoded by SEQ ID NO:101) to form a single inventive concept, and the protein as well as the nucleotide claims should be examined together in this application.

Withdrawal of the objection to claims 23 and 24 is therefore respectfully requested.

Utility rejections under 35 U.S.C. § 101 and 35 U.S.C. § 112, first paragraph:

The rejection of claims 23-29 and 31 under 35 U.S.C. § 101 and 35 U.S.C. § 112, first paragraph, as allegedly lacking a specific, substantial, and credible utility was maintained. The rejection of claims 1, 21, and 33 is improper, as the inventions of those claims have a patentable utility as set forth in the instant specification, and/or a utility well known to one of ordinary skill in the art.

The Final Office Action includes arguments made and positions taken for the first time in a misplaced attempt to justify the rejections of the claims under 35 U.S.C. §§ 101 and 112. This is particularly so with respect to the specific, substantial, and credible utilities disclosed in the Tang '260 application (to which the instant application claims priority) relating to the use of the SEQ ID NO:22-encoding polynucleotides for gene expression monitoring applications. Such gene expression monitoring applications are highly useful in drug development and in toxicity testing.

The Final Office Action's new positions and arguments include that (a) the use of the claimed polynucleotides in monitoring gene expression is "not specific" (Final Office Action, e.g., pages 7-8); and (b) the gene expression monitoring results obtained using the claimed SEQ ID NO:22-encoding polynucleotides are allegedly "not ... informative" or otherwise insufficient to constitute substantial, specific and credible utilities for the SEQ ID NO:1 polypeptide (Final Office Action, e.g., page 5). The Final Office Action further asserts that the previously submitted references describing gene expression profiling, such as Rockett et al., and Lashkari et al. allegedly support the Examiner's assertion that "the use of the claimed polynucleotides in either microarrays or gene expression monitoring merely constitutes further research to determine the significance of the claimed nucleic acid itself" (Final Office Action, page 9).

Under the circumstances, Applicants are submitting with this Response to Final Office Action the Declaration of John C. Rockett, Ph.D., under 37 C.F.R. § 1.132, with attached Exhibits A - Q; the Declaration of Vishwanath R. Iyer, Ph.D., under 37 C.F.R. § 1.132 with Exhibits A-E; the Second Declaration of Tod Bedilion, Ph.D., under 37 C.F.R. § 1.132; and ten references published before the May 29, 1998 priority date of the instant application. As we will show, the Rockett Declaration, the Iyer Declaration, the Second Bedilion Declaration, and the accompanying references show the many substantial reasons why the Final Office Actions's new positions and arguments with respect to the use

of the claimed SEQ ID NO:22-encoding polynucleotides in gene expression monitoring applications are without merit.

The fact that the Rockett, Iyer, and Second Bedilion Declarations, along with the accompanying references, are being submitted in response to positions taken and arguments made for the first time in the Final Office Action, including arguments disregarding the persuasiveness of the First Bedilion Declaration, constitutes by itself "good and sufficient reasons" under 37 C.F.R. § 1.195 why these Declarations and references were not earlier submitted and should be admitted at this time. Appellants also note that the submitted Declarations and references are responsive to the new utility rejection as framed by the Board of Appeals in copending cases with similar issues.

A. Specific uses of the claimed polynucleotides in expression profiling and toxicology testing were well-established prior to Applicants' filing date

The Final Office Action states that the asserted utilities for the claimed polypeptides in expression profiling are "not specific," and that the results of expression monitoring assays using the claimed polynucleotides allegedly "would not be informative" (Final Office Action, page 5).

Applicants submit three additional expert Declarations under 37 C.F.R. § 1.132, with respective attachments, and ten (10) scientific references filed before the May 29, 1998 priority date of the instant application. The First Bedilion Declaration, Rockett Declaration, Iyer Declaration, Second Bedilion Declaration, and the ten (10) references fully establish that, prior to the May 29, 1998 filing date of the parent Tang '260 application, it was well-established in the art that:

> polynucleotides derived from nucleic acids expressed in one or more tissues and/or cell types can be used as hybridization probes -- that is, as tools -- to survey for and to measure the presence, the absence, and the amount of expression of their cognate gene;
>
> with sufficient length, at sufficient hybridization stringency, and with sufficient wash stringency -- conditions that can be routinely established -- expressed polynucleotides, used as probes, generate a signal that is specific to the cognate gene, that is, produce a gene-specific expression signal;
>
> expression analysis is useful, *inter alia*, in drug discovery and lead optimization efforts, in toxicology, particularly toxicology studies conducted early in

drug development efforts, and in phenotypic characterization and categorization of cell types, including neoplastic cell types;

each additional gene-specific probe used as a tool in expression analysis provides an additional gene-specific signal that could not otherwise have been detected, giving a more comprehensive, robust, higher resolution, statistically more significant, and thus more useful expression pattern in such analyses than would otherwise have been possible;

biologists, such as toxicologists, recognize the increased utility of more comprehensive, robust, higher resolution, statistically more significant results, and thus want each newly identified expressed gene to be included in such an analysis;

nucleic acid microarrays increase the parallelism of expression measurements, providing expression data analogous to that provided by older, lower throughput techniques, but at substantially increased throughput;

accordingly, when expression profiling is performed using microarrays, each additional gene-specific probe that is included as a signaling component on this analytical device increases the detection range, and thus versatility, of this research tool;

biologists, such as toxicologists, recognize the increased utility of such improved tools, and thus want a gene-specific probe to each newly identified expressed gene to be included in such an analytical device;

the industrial suppliers of microarrays recognize the increased utility of such improved tools to their customers, and thus strive to improve salability of their microarrays by adding each newly identified expressed gene to the microarrays they sell;

it is not necessary that the biological function of a gene be known for measurement of its expression to be useful in drug discovery and lead optimization analyses, toxicology, or molecular phenotyping experiments;

failure of a probe to detect changes in expression of its cognate gene does not diminish the usefulness of the probe as a research tool; and

failure of a probe completely to detect its cognate transcript in any single expression analysis experiment does not deprive the probe of usefulness to the community of users who would use it as a research tool.

In his Second Declaration, Dr. Bedilion explains why a person of skill in the art in 1998 would have understood that any expressed polynucleotide is useful for gene expression monitoring applications using cDNA microarrays. (Second Bedilion Declaration, e.g., ¶¶ 4-7.) In his Declaration, Dr. Iyer explains why a person of skill in the art in 1998 would have understood that any expressed polynucleotide is useful for gene expression monitoring applications using cDNA microarrays, stating that "[t]o provide maximum versatility as a research tool, the microarray should include – and as a biologist I would want my microarray to include – each newly identified gene as a probe." (Iyer Declaration, ¶ 9.)

Further evidence of the well-established utility of all expressed polypeptides and polynucleotides in toxicology testing is found in U.S. Pat. No. 5,569,588 (Reference No. 5) and published PCT applications WO 95/21944 (Reference No. 1), WO 95/20681 (Reference No. 2), and WO 97/13877 (Reference No. 7).

WO 95/21944 ("Differentially expressed genes in healthy and diseased subjects"), published August 17, 1995, describes the use of microarrays in expression profiling analyses, emphasizing that *patterns* of expression can be used to distinguish healthy tissues from diseased tissues and that *patterns* of expression can additionally be used in drug development and toxicology studies, without knowledge of the biological function of the encoded gene product. In particular, and with emphasis added:

> The present invention involves . . . methods for diagnosing diseases . . . characterized by the presence of [differentially expressed] . . . genes, despite the absence of knowledge about the gene or its function. The methods involve the use of a composition suitable for use in hybridization which consists of a solid surface on which is immobilized at pre-defined regions thereon a plurality of defined oligonucleotide/ polynucleotide sequences for hybridization. Each sequence comprises a fragment of an EST. . . . Differences in hybridization patterns produced through use of this composition and the specified methods enable diagnosis of diseases based on differential expression of genes of unknown function. . . . [abstract]

> The method [of the present invention] involves producing and comparing hybridization patterns formed between samples of expressed mRNA or cDNA polynucleotide sequences . . . and a defined set of oligonucleotide/polynucleotide[] . . . immobilized on a support. Those defined [immobilized] oligonucleotide/polynucleotide sequences are representative of the total expressed genetic component of the cells,

tissues, organs or organism as defined by the collection of partial cDNA sequences (ESTs). [page 2]

The present invention meets the unfilled needs in the art by providing methods for the . . . use of gene fragments and genes, even those of unknown full length sequence and unknown function, which are differentially expressed in a healthy animal and in an animal having a specific disease or infection by use of ESTs derived from DNA libraries of healthy and/or diseased/infected animals. [page 4]

Yet another aspect of the invention is that it provides . . . a means for . . . monitoring the efficacy of disease treatment regimes including . . . toxicological effects thereof." [page 4]

It has been appreciated that one or more differentially identified EST or gene-specific oligonucleotide/polynucleotides define a pattern of differentially expressed genes diagnostic of a predisease, disease or infective state. A knowledge of the specific biological function of the EST is not required only that the EST[] identifies a gene or genes whose altered expression is associated reproducibly with the predisease, disease or infectious state. [page 4]

As used herein, the term 'disease' or 'disease state' refers to any condition which deviates from a normal or standardized healthy state in an organism of the same species in terms of differential expression of the organism's genes. . . [whether] of genetic or environmental origin, for example, an inherited disorder such as certain breast cancers. . . .[or] administration of a drug or exposure of the animal to another agent, e.g., nutrition, which affects gene expression. [page 5]

As used herein, the term 'solid support' refers to any known substrate which is useful for the immobilization of large numbers of oligonucleotide/polynucleotide sequences by any available method . . . [and includes, inter alia,] nitrocellulose, . . . glass, silica. . . . [page 6]

By 'EST' or 'Expressed Sequence Tag' is meant a partial DNA or cDNA sequence of about 150 to 500, more preferably about 300, sequential nucleotides. . . . [page 6]

One or more libraries made from a single tissue type typically provide at least about 3000 different (i.e., unique) ESTs and potentially the full complement of all possible ESTs representing all cDNAs e.g., 50,000 100,000 in an animal such as a human. [page 7]

The lengths of the defined oligonucleotide/ polynucleotides may be readily increased or decreased as desired or needed. . . . The length is generally guided by the

principle that it should be of sufficient length to insure that it is on[] average only represented once in the population to be examined. [page 7]

Comparing the . . . hybridization patterns permits detection of those defined oligonucleotide/ polynucleotides which are differentially expressed between the healthy control and the disease sample by the presence of differences in the hybridization patterns at pre-defined regions [of the solid support]. [page 13]

It should be appreciated that one does not have to be restricted in using ESTs from a particular tissue from which probe RNA or cDNA is obtained[;] rather any or all ESTs (known or unknown) may be placed on the support. Hybridization will be used [to] form diagnostic patterns or to identify which particular EST is detected. For example, all known ESTs from an organism are used to produce a 'master' solid support to which control sample and disease samples are alternately hybridized. [page 14]

Diagnosis is accomplished by comparing the two hybridization patterns, wherein substantial differences between the first and second hybridization patterns indicate the presence of the selected disease or infection in the animal being tested. Substantially similar first and second hybridization patterns indicate the absence of disease or infection. This[,] like many of the foregoing embodiments[,] may use known or unknown ESTs derived from many libraries. [page 18]

Still another intriguing use of this method is in the area of monitoring the effects of drugs on gene expression, both in laboratories and during clinical trials with animal[s], especially humans. [page 18]

WO 95/20681 ("Comparative Gene Transcript Analysis"), filed in 1994 by Appellants' assignee and published August 3, 1995, has three issued U.S. counterparts: U.S. Pat. Nos. 5,840,484, issued November 24, 1998; 6,114,114, issued September 5, 2000; and 6,303,297, issued October 16, 2001.

The specification describes the use of transcript expression *patterns,* or "images", each comprising multiple pixels of gene-specific information, for diagnosis, for cellular phenotyping, and in toxicology and drug development efforts. The specification describes a plurality of methods for obtaining the requisite expression data -- one of which is microarray hybridization -- and equates the uses of the expression data from these disparate platforms. In particular, and with emphasis added:

The invention provides a "method and system for quantifying the relative abundance of gene transcripts in a biological specimen. . . . [G]ene transcript imaging can be used to detect or diagnose a particular biological state, disease, or condition which is

correlated to the relative abundance of gene transcripts in a given cell or population of cells. The invention provides a method for comparing the gene transcript image analysis from two or more different biological specimens in order to distinguish between the two specimens and identify one or more genes which are differentially expressed between the two specimens." [abstract]

"[W]e see each individual gene product as a 'pixel' of information, which relates to the expression of that, and only that, gene. We teach herein [] methods whereby the individual 'pixels' of gene expression information can be combined into a single gene transcript 'image,' in which each of the individual genes can be visualized simultaneously and allowing relationships between the gene pixels to be easily visualized and understood." [page 2]

"The present invention avoids the drawbacks of the prior art by providing a method to quantify the relative abundance of multiple gene transcripts in a given biological specimen. . . . The method of the instant invention provides for detailed diagnostic comparisons of cell profiles revealing numerous changes in the expression of individual transcripts." [page 6]

"High resolution analysis of gene expression be used directly as a diagnostic profile. . . . " [page 7]

"The method is particularly powerful when more than 100 and preferably more than 1,000 gene transcripts are analyzed." [page 7]

"The invention . . . includes a method of comparing specimens containing gene transcripts." [page 7]

"The final data values from the first specimen and the further identified sequence values from the second specimen are processed to generate ratios of transcript sequences, which indicate the differences in the number of gene transcripts between the two specimens." [i.e., the results yield analogous data to microarrays] [page 8]

"Also disclosed is a method of producing a gene transcript image analysis by first obtaining a mixture of mRNA, from which cDNA copies are made." [page 8]

"In a further embodiment, the relative abundance of the gene transcripts in one cell type or tissue is compared with the relative abundance of gene transcript numbers in a second cell type or tissue in order to identify the differences and similarities." [page 9]

"In essence, the invention is a method and system for quantifying the relative abundance of gene transcripts in a biological specimen. The invention provides a method for comparing the gene transcript image from two or more different biological specimens in order to distinguish between the two specimens. . . . " [page 9]

"[T]wo or more gene transcript images can be compared and used to detect or diagnose a particular biological state, disease, or condition which is correlated to the relative abundance of gene transcripts in a given cell or population of cells." [pages 9 10]

"The present invention provides a method to compare the relative abundance of gene transcripts in different biological specimens. . . . This process is denoted herein as gene transcript imaging. The quantitative analysis of the relative abundance for a set of gene transcripts is denoted herein as 'gene transcript image analysis' or 'gene transcript frequency analysis'. The present invention allows one to obtain a profile for gene transcription in any given population of cells or tissue from any type of organism." [page 11]

"The invention has significant advantages in the fields of diagnostics, toxicology and pharmacology, to name a few." [page 12]

"[G]ene transcript sequence abundances are compared against reference database sequence abundances including normal data sets for diseased and healthy patients. The patient has the disease(s) with which the patient's data set most closely correlates." [page 12]

"For example, gene transcript frequency analysis can be used to differentiate normal cells or tissues from diseased cells or tissues. . . ." [page 12]

"In toxicology, . . . [g]ene transcript imaging provides highly detailed information on the cell and tissue environment, some of which would not be obvious in conventional, less detailed screening methods. The gene transcript image is a more powerful method to predict drug toxicity and efficacy. Similar benefits accrue in the use of this tool in pharmacology. . . . " [page 12]

"In an alternative embodiment, comparative gene transcript frequency analysis is used to differentiate between cancer cells which respond to anti-cancer agents and those which do not respond." [page 12]

"In a further embodiment, comparative gene transcript frequency analysis is used . . . for the selection of better pharmacologic animal models." [page 14]

"In a further embodiment, comparative gene transcript frequency analysis is used in a clinical setting to give a highly detailed gene transcript profile of a diseased state or condition." [page 14]

"An alternate method of producing a gene transcript image includes the steps of obtaining a mixture of test mRNA and providing a representative array of unique probes whose sequences are complementary to at least some of the test mRNAs. Next, a fixed

amount of the test mRNA is added to the arrayed probes. The test mRNA is incubated with the probes for a sufficient time to allow hybrids of the test mRNA and probes to form. The mRNA-probe hybrids are detected and the quantity determined." [page 15]

"[T]his research tool provides a way to get new drugs to the public faster and more economically." [page 36]

"In this method, the particular physiologic function of the protein transcript need not be determined to qualify the gene transcript as a clinical marker." [page 38]

"[T]he gene transcript changes noted in the earlier rat toxicity study are carefully evaluated as clinical markers in the followed patients. Changes in the gene transcript image analyses are evaluated as indicators of toxicity by correlation with clinical signs and symptoms and other laboratory results. . . . The . . . analysis highlights any toxicological changes in the treated patients." [page 39]

U.S. Pat. No. 5,569,588 ("Methods for Drug Screening") ("the '588 patent"), issued October 29, 1996, with a priority date of August 1995, describes an expression profiling platform, the "genome reporter matrix", which is different from nucleic acid microarrays. Additionally describing use of nucleic acid microarrays, the '588 patent makes clear that the utility of comparing multidimensional expression datasets is independent of the methods by which such profiles are obtained. The 588 patent speaks clearly to the usefulness of such expression analyses in drug development and toxicology, particularly pointing out that a gene's failure to change in expression level is a useful result. Thus, with emphasis added,

The invention provides "[m]ethods and compositions for modeling the transcriptional responsiveness of an organism to a candidate drug. . . . [The final step of the method comprises] comparing reporter gene product signals for each cell before and after contacting the cell with the candidate drug to obtain a drug response profile which provides a model of the transcriptional responsiveness of said organism to the candidate drug." [abstract]

"The present invention exploits the recent advances in genome science to provide for the rapid screening of large numbers of compounds against a systemic target comprising substantially all targets in a pathway [or] organism." [col. 1]

"The ensemble of reporting cells comprises as comprehensive a collection of transcription regulatory genetic elements as is conveniently available for the targeted organism so as to most accurately model the systemic transcriptional response. Suitable

ensembles generally comprise thousands of individually reporting elements; preferred ensembles are substantially comprehensive, i.e. provide a transcriptional response diversity comparable to that of the target organism. Generally, a substantially comprehensive ensemble requires transcription regulatory genetic elements from at least a majority of the organism's genes, and preferably includes those of all or nearly all of the genes. We term such a substantially comprehensive ensemble a genome reporter matrix." [col. 2]

"Drugs often have side effects that are in part due to the lack of target specificity. . . . [A] genome reporter matrix reveals the spectrum of other genes in the genome also affected by the compound. In considering two different compounds both of which induce the ERG10 reporter, if one compound affects the expression of 5 other reporters and a second compound affects the expression of 50 other reports, the first compound is, a priori, more likely to have fewer side effects." [cols. 2 - 3]

"Furthermore, it is not necessary to know the identity of any of the responding genes." [col. 3]

"[A]ny new compound that induces the same response profile as [a] . . . dominant tubulin mutant would provide a candidate for a taxol-like pharmaceutical." [col. 4]

"The genome reporter matrix offers a simple solution to recognizing new specificities in combinatorial libraries. Specifically, pools of new compounds are tested as mixtures across the matrix. If the pool has any new activity not present in the original lead compound, new genes are affected among the reporters." [col. 4]

" A sufficient number of different recombinant cells are included to provide an ensemble of transcriptional regulatory elements of said organism sufficient to model the transcriptional responsiveness of said organism to a drug. In a preferred embodiment, the matrix is substantially comprehensive for the selected regulatory elements, e.g. essentially all of the gene promoters of the targeted organism are included." [cols. 6 7]

"In a preferred embodiment, the basal response profiles are determined. . . . The resultant electrical output signals are stored in a computer memory as genome reporter output signal matrix data structure associating each output signal with the coordinates of the corresponding microtiter plate well and the stimulus or drug. This information is indexed against the matrix to form reference response profiles that are used to determine the response of each reporter to any milieu in which a stimulus may be provided. After establishing a basal response profile for the matrix, each cell is contacted with a candidate drug. The term drug is used loosely to refer to agents which can provoke a specific cellular response. . . . The drug induces a complex response pattern of repression, silence and induction across the matrix . . . .The response profile reflects the

cell's transcriptional adjustments to maintain homeostasis in the presence of the drug. . . . After contacting the cells with the candidate drug, the reporter gene product signals from each of said cells is again measured to determine a stimulated response profile. The basal o[r] background response profile is then compared with . . . the stimulated response profile to identify the cellular response profile to the candidate drug." [cols. 7 8]

"In another embodiment of the invention, a matrix [i.e., array] of hybridization probes corresponding to a predetermined population of genes of the selected organism is used to specifically detect changes in gene transcription which result from exposing the selected organism or cells thereof to a candidate drug. In this embodiment, one or more cells derived from the organism is exposed to the candidate drug in vivo or ex vivo under conditions wherein the drug effects a change in gene transcription in the cell to maintain homeostasis. Thereafter, the gene transcripts, primarily mRNA, of the cell or cells is isolated . . . [and] then contacted with an ordered matrix [array] of hybridization probes, each probe being specific for a different one of the transcripts, under conditions where each of the transcripts hybridizes with a corresponding one of the probes to form hybridization pairs. The ordered matrix of probes provides, in aggregate, complements for an ensemble of genes of the organism sufficient to model the transcriptional responsiveness of the organism to a drug. . . . The matrix-wide signal profile of the drug-stimulated cells is then compared with a matrix-wide signal profile of negative control cells to obtain a specific drug response profile." [col. 8]

"The invention also provides means for computer-based qualitative analysis of candidate drugs and unknown compounds. A wide variety of reference response profiles may be generated and used in such analyses." [col. 8]

"Response profiles for an unknown stimulus (e.g. new chemicals, unknown compounds or unknown mixtures) may be analyzed by comparing the new stimulus response profiles with response profiles to known chemical stimuli." [col. 9]

"The response profile of a new chemical stimulus may also be compared to a known genetic response profile for target gene(s)." [col. 9]

The August 11, 1997 press release from the '588 patent's assignee, Acacia Biosciences (now part of Merck) (reference "8" attached hereto), and the September 15, 1997 news report by Glaser, "Strategies for Target Validation Streamline Evaluation of Leads," *Genetic Engineering News* (reference "9" attached hereto), attest the commercial value of the methods and technology described and claimed in the '588 patent.

WO 97/13877 ("Measurement of Gene Expression Profiles in Toxicity Determinations"), published April 17, 1997, describes an expression profiling technology differing somewhat from the use of cDNA microarrays and differing from the genome reporter matrix of the '588 patent; but the use of the data is analogous. As per its title, the reference describes use of expression profiling in toxicity determinations. In particular, and with emphasis added:

> "[T]he invention relates to a method for detecting and monitoring changes in gene expression patterns in in vitro and in vivo systems for determining the toxicity of drug candidates." [Field of the invention]
>
> "An object of the invention is to provide a new approach to toxicity assessment based on an examination of gene expression patterns, or profiles, in in vitro or in vivo test systems." [page 3]
>
> "Another object of the invention is to provide a rapid and reliable method for correlating gene expression with short term and long term toxicity in test animals." [page 3]
>
> "The invention achieves these and other objects by providing a method for massively parallel signature sequencing of genes expressed in one or more selected tissues of an organism exposed to a test compound. An important feature of the invention is the application of novel . . . methodologies that permit the formation of gene expression profiles for selected tissues . . . . Such profiles may be compared with those from tissues of control organisms at single or multiple time points to identify expression patterns predictive of toxicity." [page 3]
>
> "As used herein, the terms 'gene expression profile,' and 'gene expression pattern' which is used equivalently, means a frequency distribution of sequences of portions of cDNA molecules sampled from a population of tag-cDNA conjugates. . .. Preferably, the total number of sequences determined is at least 1000; more preferably, the total number of sequences determined in a gene expression profile is at least ten thousand." [page 7]
>
> "The invention provides a method for determining the toxicity of a compound by analyzing changes in the gene expression profiles in selected tissues of test organisms exposed to the compound. . . . . Gene expression profiles derived from test organisms are compared to gene expression profiles derived from control organisms. . . . " [page 7]

Accordingly, Dr. Rockett concludes in his Declaration that:

> It is my opinion, therefore, based on the state of the art in toxicology at least since the mid-1990s . . . that disclosure of the sequence of a new gene or protein, with or without knowledge of its biological function, would have been sufficient information for a toxicologist to use the gene and/or protein in expression profiling studies in toxicology.[1] [Rockett Declaration, ¶ 18.]

B. Applicants' showing of facts overcomes the Examiner's concern that Applicants' invention lacks "specific utility"

The Final Office Action alleges that "applicants have disclosed no features or characteristics of the claimed nucleotides encoding SEQ ID NO:22 or nucleotides of SEQ ID NO:101 that would inform the experimenter as to what the significance of detecting that particular sequence would be" and that the use of the claimed polynucleotides in cDNA microarrays is allegedly "the very definition of a *non-specific utility*" (Final Office Action, pages 7-8).

Applicants' submission of additional facts overcomes this concern. Those facts demonstrate that, far from applying ***regardless*** of the specific properties of the claimed invention, the utility of Appellants' claimed polynucleotides as gene-specific probes ***depends upon*** specific properties of the polynucleotides, that is, their nucleic acid sequences.

"[E]ach probe on . . . [a "high density spotted microarray[]"], with careful design and sufficient length, and with sufficiently stringent hybridization and wash conditions, ***binds specifically*** and with minimal cross-hybridization, to the probe's cognate transcript"[2]; "[e]ach gene included as a probe on a microarray provides ***a signal that is specific to the cognate transcript***, at least to a first approximation."[3] Accordingly, "each additional probe makes an additional transcript newly detectable by the microarray, increasing the detection range, and thus versatility, of this analytical device for gene

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"Use of the words 'it is my opinion' to preface what someone of ordinary skill in the art would have known does not transform the factual statements contained in the declaration into opinion testimony." *In re Alton*, 37 USPQ2d 1578, 1583 (Fed. Cir. 1996).

[2] Declaration of Dr. John C. Rockett, ¶ 10(i), emphasis added.

[3] Declaration of Dr. Vishwanath R. Iyer, ¶ 7 (emphasis added). See the footnote at ¶ 7 for a slightly more "nuanced" view.

expression profiling"[4]; equally, "[e]ach new gene-specific probe added to a microarray thus increases the number of genes detectable by the device, increasing the resolving power of the device."[5]

Although not required for present purposes, it would be appropriate to state on the record here that the specificity of nucleic acid hybridization was well-established far earlier than the development of high density spotted microarrays in 1995, and indeed is the well-established underpinning of many, perhaps most, molecular biological techniques developed over the past 30 - 40 years.

The Final Office Action agrees that toxicology testing is "a well-established use of polynucleotides and the polypeptides encoded" (Final Office Action, page 10), but asserts that "this is a utility that is non-specific and would apply to virtually every member of a class of materials, such as proteins or DNA" (Final Office Action, page 11). Applicants respectfully point out that it is not the case that all DNA molecules would be useful for toxicology testing, only those polynucleotides which are naturally expressed in humans. A random DNA sequence not found in nature, for example, would lack such utility.

While it is true that all polynucleotides expressed in humans have utility in toxicology testing based on the property of being expressed at some time in development or in the cell life cycle, this basis for utility does not preclude that utility from being specific and substantial. A toxicology test using any particular expressed polypeptide or polynucleotide is dependent on the **identity** of that polypeptide or polynucleotide, not on its biological function or its disease association. The results obtained from using any particular human-expressed polypeptide or polynucleotide in toxicology testing is specific to both the compound being tested and the polypeptide or polynucleotide used in the test. **No two human-expressed polypeptides or polynucleotides are interchangeable for toxicology testing** because the effects on the expression of any two such polypeptides or polynucleotides will differ depending on the identity of the compound tested and the **identities** of the two polypeptides or polynucleotides. It is not necessary to know the biological functions and disease associations of the polypeptides or polynucleotides in order to carry out such toxicology tests. Therefore, at the very least,

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4 Declaration of Dr. John C. Rockett, ¶ 10(ii).

5 Declaration of Dr. Vishwanath R. Iyer, ¶ 7.

the claimed polynucleotides are specific controls for toxicology tests in developing drugs targeted to other polypeptides or polynucleotides, and are clearly useful as such.

C. The Rockett and Lashkari references demonstrate that use of the claimed polynucleotides in expression profiling does not merely constitute further research on the claimed polynucleotides themselves

The Final Office Action asserts that the Rockett et al. and Lashkari et al. references submitted with the Response to Office Action filed June 24, 2003 allegedly teach that "the use of the claimed polynucleotides in either microarrays or gene expression monitoring merely constitutes further research to determine the significance of the claimed nucleic acid itself" (Final Office Action, page 9).

The Final Office Action first states that "these references, e.g, Rockett et al. and Lashkari et al. have not been previously cited or discussed on the record, nor have applicants in any information disclosure statement made them of record" (Final Office Action, page 8). Applicants note that the Rockett et al. paper (Xenobiotica, 1999 29:655-691) and the Lashkari et al. paper (Proc. Nat. Acad. Sci. U.S.A., 1997, 94:8945-8947) were submitted with the Response to Office Action filed June 24, 2003, to provide evidence of the utility of the claimed invention in gene expression monitoring for toxicology testing. The Examiner is obliged to consider evidence provided by Applicants in support the patentability of the claims.

> Once a prima facie showing of no specific and substantial credible utility has been properly established, the applicant bears the burden of rebutting it. The applicant can do this by amending the claims, by providing reasoning or arguments, or by **providing evidence in the form of a declaration under 37 CFR 1.132 or a patent or a printed publication that rebuts the basis or logic of the prima facie showing. If the applicant responds to the prima facie rejection, the Office personnel should review the original disclosure, any evidence relied upon in establishing the prima facie showing, any claim amendments, and any new reasoning or evidence provided by the applicant in support of an asserted specific and substantial credible utility. It is essential for Office personnel to recognize, fully consider and respond to each substantive element of any response to a rejection based on lack of utility.** Only where the totality of the record continues to show that the asserted utility is not specific, substantial, and credible should a rejection based on lack of utility be maintained. (MPEP, § 2107 II. D., emphasis added.)

The Final Office Action next alleged that the Rockett et al. (Reference No. 1 cited in the Response filed June 24, 2003) and Lashkari et al. (Reference No. 2 cited in the Response filed June 24, 2003) articles teach that use of a polynucleotide in microarrays is useful only for further characterization of the detected genes and probes themselves (Final Office Action, pages 8-10). The Final Office Action quoted the first sentence of the Rockett et al. abstract: "[a]n important feature of the work of many molecule [*sic*: molecular] biologists is identifying which genes are turned on and off in a cell under different environmental conditions of [*sic*: or] or subsequent to xenobiotic challenge. **Such information has many uses, including the deciphering of molecular pathways and facilitating the development of new experimental and diagnostic procedures.**" (Final Office Action, page 9, emphasis given in Final Office Action.) The Examiner reads this sentence narrowly, suggesting that the Rockett et al. article teaches that the **only uses** for cDNA microarrays are for further characterization of the detected genes and probes. However, reading further than the first sentence of the Rockett et al. article's abstract, Applicants note that the authors expand the possible uses of differential gene expression analysis, stating that:

> Differential gene display provides a coherent platform for building libraries and microchip arrays of 'gene fingerprints' characteristic of known enzyme inducers and xenobiotic toxicants, which may be interrogated subsequently **for the identification and characterization of xenobiotics of unknown biological properties.** (Rockett et al., abstract, page 655, emphasis added.)

Rockett et al. teach that "in the field of chemical-induced toxicity, it is now becoming increasingly obvious that most adverse reactions to drugs and chemicals are the result of multiple gene regulation, some of which are causal and some of which are casually-related to the toxicological phenomenon *per se*. This observation has led to an upsurge in interest in gene-profiling technologies which differentiate between the control and toxin-treated gene pools in target tissues and is therefore, of value in rationalizing the molecule mechanisms of xenobiotic-induced toxicity (Rockett, page 656, emphasis in original). Rockett et al. thus teach that microchip analyses are useful for the "identification and characterization of xenobiotics of unknown biological properties," in addition to those uses in "deciphering of molecular pathways and facilitating the development of new experimental and diagnostic procedures. The Examiner has ignored these teachings in the discussion in the Final Office Action.

The Final Office Action further alleges that the Lashkari et al. article (Reference No. 2 cited in the Response filed June 24, 2003) teaches that "sequences of unknown function or significance are used in such strategies [microarrays] *to learn more about the sequences themselves and the genes they represent*" (Final Office Action, page 10, emphasis in original). The Final Office Action cites several lines from the first page of the Lashkari et al. article. Reading further into the article, Applicants respectfully note that Lashkari et al. teach broader uses for cDNA microarrays that the narrow reading adopted by the Examiner. For example, whole genome analysis is useful because it allows one to "analyze numerous genes under many conditions" (Lashkari et al., page 8946). In addition, Lashkari et al. teach that data from genome projects will not only allow one "to gain a truly comprehensive understanding of gene function" but also "more broadly, of the entire genome" (Lashkari et al., page 8947). Furthermore, such understanding "should come from the viewpoint of the integration of complex regulatory networks, the individual roles and interactions of thousands of functional gene products, and the effect of environmental changes on both gene regulatory networks and the roles of all gene products. The time has come to switch from the analysis of a single gene to the analysis of the whole genome" (Lashkari et al, page 8947). Hence, the Lashkari et al. article supports the utility of open reading frames (ORFs) in whole genome analysis by cDNA microarrays and in particular, for determining the "effect of environmental changes on gene regulatory networks and the roles of all gene products" (Lashkari et al., page 8947).

Furthermore, Applicants have submitted with this Response the Declaration of John C. Rockett, who is the first author of the Rockett paper. Dr. Rockett himself points out that his article describes how gene expression profiling is useful in toxicology, quoting several pertinent paragraphs (Rockett Declaration, ¶ 15). Dr. Rockett concludes that: "In the context of such *patterns* of gene expression, each additional gene-specific probe provides an additional signal that could not otherwise have been detected, giving a more comprehensive, robust, higher resolution -- and thus more useful -- pattern than otherwise would have been possible.[6]" (Rockett Declaration, ¶¶ 16-17).

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[6] In a sense, each gene-specific probe used in such an analysis is analogous to a different one of the many parts of an engine, with each individual part, or subcombinations of such parts, deriving at least part of their usefulness from the utility of the completed combination, the functioning engine.

The Iyer Declaration provides additional examples of uses for the claimed nucleotides in microarrays, including toxicology testing and classification of human tumor cell lines (Iyer Declaration, ¶ 5). As Dr. Iyer points out, "each new gene probe added to a microarray increases the usefulness of the device in gene expression profiling analyses" (Iyer Declaration, ¶ 7), by increasing the resolving power of the array. This increased resolution provides results, such as subdivisions of otherwise indistinguishable cancers into a greater number of classes, permitting better individualizing of therapy, that are simply not available with less complete arrays (Iyer Declaration, ¶ 8).

Dr. Iyer explicitly states that "these pattern-based analyses do not require knowledge of the biological function of the encoded proteins" (Iyer Declaration, ¶ 5). Dr. Rockett concurs that "disclosure of the sequence of a new gene or protein, with or without knowledge of its biological function, would have been sufficient information for a toxicologist to use the gene and/or protein in expression profiling studies in toxicology" (Rockett Declaration, ¶ 18). Thus there is no need to show that SEQ ID NO:101 has identical expression patterns to a known cancer marker or is a surrogate for a cell protein of interest in toxicology, as asserted in the Final Office Action (page 16).

For these reasons, the claimed sequences are not analogous to the compounds of *Brenner v Manson*, as the Final Office Action attempts to argue (Final Office Action, page 15). The claimed sequences do not merely have a "substantial likelihood" of being useful, or a good probability of being "*eventually* shown to be useful for *something*" (Final Office Action, pages 14-15). Rather, they are useful **today**, in the real world, for specific, substantial and credible uses in, for example, toxicology testing and discrimination between cancer subtypes.

D. Use of the claimed polynucleotides in toxicology testing

The Final Office Action asserts that the First Bedilion Declaration is insufficient to overcome the utility rejection "because the instant specification provides general methods and no specific examples" (Final Office Action, page 6). The Final Office Action further asserts that "no demonstration of the use of specific SEQ IDs for the purpose of detecting differential expression and in the use for diagnosis is provided" (Final Office Action, page 7).

These arguments amount to nothing more than the Examiner's disagreement with the First Bedilion Declaration and the Applicants' assertions about the knowledge of a person of ordinary skill in the art, and is tantamount to the substitution of the Examiner's own judgment for that of the Applicants' expert. The Examiner must accept the Applicants' assertions to be true. The Examiner is, moreover, wrong on the facts because the First Bedilion Declaration demonstrates how one of skill in the art, reading the specification at the time the Tang '260 application was filed (May 29, 1998), would have understood that specification to disclose the use of the claimed polynucleotides in gene expression monitoring for toxicology testing, drug development, and the diagnosis of disease (See the First Bedilion Declaration at, e.g., ¶¶ 10-16).

Nowhere does the Final Office Action address the fact that, as described on page 55 of the Tang '590 application, the claimed polynucleotides can be used as highly specific probes in, for example, cDNA microarrays – probes that without question can be used to measure both the existence and amount of complementary RNA sequences known to be the expression products of the claimed polynucleotides. The specification makes clear that "oligonucleotides or longer fragments derived from any of the polynucleotide sequences described herein may be used as targets in a microarray" (specification, page 55, lines). These described polynucleotide sequences clearly include SEQ ID NO:101 (see the specification, page 12, line 18) and polynucleotides encoding SEQ ID NO:22 (specification, page 12, lines 1-2), polynucleotide variants having at least 90% polynucleotide sequence identity to SEQ ID NO:101 (specification, page 12, line 32 through page 13, line 2) and polynucleotides having at least 90% identity to polynucleotides encoding SEQ ID NO:22 (specification, page 26, lines 27-30).

The claimed invention is not some random sequence whose value as a probe is speculative or would require further research to determine. For example, monitoring the expression of the SEQ ID NO:22-encoding polynucleotides is a method of testing the toxicology of drug candidates during the drug development process. Dr. Bedilion in his First Declaration states that "good drugs are not only potent, they are specific. This means that they have strong effects on a specific biological target and minimal effects on all other biological targets" (First Bedilion Declaration ¶ 10). Thus, if the expression of a particular polynucleotide is affected in any way by exposure to a test compound, and if that

particular polynucleotide is not the specific target of the test compound (e.g., if the test compound is a drug candidate), then the change in expression is an indication that the test compound has undesirable toxic side effects. It is important to note that such an indication of possible toxicity is specific not only for each compound tested, but also for each and every individual polynucleotide whose expression is being monitored.

However, the Examiner continues to view the utility in toxicology testing of the claimed polynucleotides as requiring knowledge of either the biological function or disease association of the claimed polynucleotides. The Examiner views toxicology testing as a process to measure the toxicity of a drug candidate only when that drug candidate is specifically targeted to the claimed polynucleotides. The Examiner has refused to consider that the claimed polynucleotides are useful for measuring the toxicity of drug candidates which are targeted not to the claimed polynucleotides, but to **other** polynucleotides. This utility of the claimed polynucleotides does not require any knowledge of the biological function or disease association of the SEQ ID NO:22 polypeptide or SEQ ID NO:101 polynucleotide and is a specific, substantial and credible utility.

E. The similarity of the polypeptide encoded by the claimed invention to another polypeptide of undisputed utility also demonstrates utility

In addition to the described utilities in toxicology testing and expression profiling, which do not require any knowledge of the biological function or disease association of the claimed polynucleotides, the claimed polynucleotides **also** have utility based upon the similarity of the encoded polypeptide to another polypeptide of undisputed utility. The specification as filed identified HTMPN-22 as a Ring3-related bromodomain (see pages 88 and 107 of the specification, as well as the BLAST search and MOTIFS analyses (Exhibits A and B) submitted with the Response to Office Action filed June 24, 2003). In that Response, Applicants also submitted the Ocstrowski reference, which disclosed that prior to the time of filing, the RING3 kinase was known to be very active in leukocytes of patients with acute and chronic leukemias, and "[i]n one leukemic patient in remission the activity of the RING3 kinase in leukocytes returned to normal, suggesting that RING3 kinase may be involved in the pathogenesis of the disease (Ostrowski, page 1223, col. 2). The Ostrowski paper further disclosed

that "systemic administration of mitogenic and inflammatory agents into mice stimulates activity of p85/RING3 kinase in a number of organs" (Ostrowski, page 1226, col. 2).

The Final Office Action acknowledges that the Ocstrowski resference teaches a specific utility, based upon the protein's role in leukemias, but asserts that this utility is "not substantial," because the use is allegedly only "speculative" (Final Office Action pages 11-12). Applicants respectfully point out that the association of RING3 with leukemia is not at all speculative, but a matter of fact. The particular biological function of RING3 in causing the disease may not be known, but the correlation of activity levels of RING3 with leukemia is a well-known fact. The Final Office Action has stated that it is untrue that the Patent Office is requiring a specific biological function for the claimed sequences, stating that "the mere correlation of the presence of the nucleic acid, in a manner that would be found to be credible by a person of ordinary skill in the art, with the presence of a disease or condition would clearly meet the requirements of 35 U.S.C. § 101" (Final Office Action, page 6). **Such an association, correlating increased RING3 activity levels with leukemia and decreased levels with remission of the disease, is precisely what is taught in the Ocstrowski paper**.

The Final Office Action then argues that the homology of HTMPN-22 with RING3 is too low to be certain that the claimed protein has the same function as RING3 (Final Office Action, page 12). In support of this assertion, the Final Office Action cites only the Scott reference. The reasons why the Scott reference would fail to convince one of skill in the art that HTMPN-22 was not related to RING3 were discussed in the Response to Office Action filed June 24, 2003. The Final Office Action does not dispute that HTMPN-22 is a member of the RING3 family, but asserts that membership in a gene family is not enough, absent a specific, substantial and credible utility (Final Office Action, page 12). This assertion appears to miss the point -- the fact that HTMPN-22 is a member of the RING3 family demonstrates utility because **all** the members of this particular family have utility for the diagnosis of cell proliferative disorders. In fact, the Final Office Action acknowledges that postfiling art (the French and Maruyama references) confirms that other members of the family, such as BRD4, are also associated with cancers (Final Office Action, page 13). In fact, the French reference discloses that the long form of BRD4 is almost identical to SEQ ID NO:101 (99.2% sequence identity). One of skill in the art

would clearly understand that the claimed sequences encoding HTMPN-22, as well as the claimed 90% variants of these sequences, would have utility in the diagnosis of cancer.

The Final Office Action further asserts that the specification does not recite that HTMPN-22 is specifically involved either in cancer or the diagnosis of cancer (Final Office Action, page 13). As discussed above, one of skill in the art would readily understand, based upon the disclosure in the specification identifying HTMPN-22 as a RING3-related bromodomain protein, that HTMPN-22 would be associated with cancer and therefore useful in the diagnosis of cancer. In addition, the specification does disclose that HTMPN-22 is specifically associated with cancer. For example, northern analysis of SEQ ID NO:101 shows its expression predominantly in cDNA libraries associated with cancer, inflammation and the immune response, and fetal development (see Table 3, specification at page 88). Moreover, sequences encoding SEQ ID NO:22 were initially isolated from a brain tumor library (Table 4, specification at page 97). Thus one of skill in the art would have understood at the time of filing that polynucleotides encoding HTMPN-22 would be expected to have utility in the diagnosis of cancers, as described in the specification at, for example, page 53, lines 14-24, or page 54, lines 19-25. One of skill in the art would immediately understand that the fact that these particular lines recite the HTMPN molecules as a group rather than listing them all individually does not mean that the utility described does not apply to each of the HTMPN molecules (including HTMPN-22) individually, as well as to the group as a whole.

F. The asserted utility in toxicology testing and expression profiling also applies to the claimed polynucleotide variants.

The Final Office Action asserts that the asserted utility for the claimed polynucleotides in toxicology testing and expression profiling would only apply to the exact, naturally occurring sequence and not to nucleic acids which vary by codon degeneracy or to nucleic acids having at least 90% identity to the exact sequence (Final Office Action, pages 4-5). Applicants respectfully point out that nucleic acids which vary by codon degeneracy from SEQ ID NO:101 will still encode the amino acid sequence of SEQ ID NO:22. As described in the Rockett Declaration (¶¶ 11-14, and attached Exhibits L-Q), naturally occurring protein sequences such as SEQ ID NO:22 are also useful in

expression profiling and toxicology testing. Thus any sequence which encodes SEQ ID NO:22 is useful for the production of SEQ ID NO:22 for use in such applications. Applicants further note that the recited variants of SEQ ID NO:101 are all naturally occurring, and thus share the same utilities as other naturally occurring polynucleotides such as SEQ ID NO:101 in expression profiling and toxicology testing. For this reason, it does not matter if they do not specifically recognize SEQ ID NO:101, since they will recognize their own complementary nucleic acids.

Written description rejections under 35 U.S.C. § 112, first paragraph:

The rejection of claims 23-29 and 31 under 35 U.S.C. § 112, first paragraph as allegedly lacking adequate written description was maintained. The Final Office Action acknowledges that the specification has described SEQ ID NO:101, which encodes the amino acid sequence of SEQ ID NO:22. For this reason, Applicants respectfully submit that the written description rejection does not apply to claims 24, 25, and 29, which recite only SEQ ID NO:101 or polynucleotide sequences which encode SEQ ID NO:22.

With respect to the claimed nucleic acid variants, the Final Office Action asserts that Applicants have provided no information about how conserved the gene is, how similar the homologues from other species would be expected to be, or provided description of the function of the gene or encoded protein so as to indicate which portions of the sequence would be expected to be conserved (Final Office Action, page 20). As set forth in the Response to Office Action filed June 24, 2003, the claims of the subject application are fundamentally different from those found invalid in *Lilly* and *Fiers*. The subject matter of the present claims is defined in terms of the chemical structure of SEQ ID NO:22 or SEQ ID NO:101. The courts have stressed that structural features are important factors to consider in a written description analysis of claims to nucleic acids. Thus a description of the function of the gene or encoded protein is not required. In addition, the genus of DNA defined by the present claims is not "highly variant," as evidenced by the previously submitted Brenner et al. paper (Reference No. 8 in the Response to Office Action filed June 24, 2003). Furthermore, there have been remarkable advances in the state of the art since the *Lilly* and *Fiers* cases, and these advances were given no consideration whatsoever in the position set forth by the Office Action.

The Examiner attempts to distinguish the *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993) and *University of California v. Eli Lilly and Co.*, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997) cases from the instant case as "the claims in both those cases were limited to the naturally occurring sequences encoding particular proteins, which proteins are well known by their functions" and that "[i]n this case, Applicants claims required no such conserved function" (Final Office Action, page 23). In *Fiers*, the Examiner contends, "the person of ordinary skill in the art would immediately recognize that any and all species within the metes and bounds of 'A DNA which consists essentially of a DNA which codes for a human fibroblast interferon-beta polypeptide,' would encode proteins with *greater* than the 90% identity claimed by Applicants; the person of ordinary skill in the art would not expect to find that great an amount of variation within a single species, while still meeting the functional limitation of being a human fibroblast interferon-beta polypeptide" (Final Office Action, page 23, emphasis in original). Applicants note first that the Examiner has provided only personal opinion to support this argument, without either evidence or sound scientific reasoning. Second, in the instant case the claimed species are described by not only their comprising "naturally-occurring" sequences but also by their percentage sequence identity with either SEQ ID NO:22 or SEQ ID NO:101. A structure is provided in the instant case by the recitation of a particular nucleotide or amino acid sequence, while it was not in the *Fiers* and *Lilly* claims.

Regarding the arguments related to the Brenner et al. reference, the Final Office Action contends that "[w]hile 90% identity is certainly sufficient to establish that two proteins are structurally similar and/or evolutionarily related, it is not predictive of function" (Final Office Action, page 25). As the claimed variants are not described by their having the same "function" as SEQ ID NO:22 or SEQ ID NO:101, the Examiner's arguments are not relevant to the written description issue. Applicants respectfully note that the Brenner reference was not presented in order to demonstrate that the claimed polynucleotides all have a conserved function, but to demonstrate that the claimed genus is not highly variant, a point which the Final Office Action does not rebut.

The Final Office Action alleges that "it is not true that one could find in nature any and all possible changes within a given gene, and the specification has described not a single naturally occurring variant of SEQ ID NO:4. . . not a single sequence disclosed that is obtained from another biological

species" (Final Office Action, page 21). Applicants are not claiming "any and all possible changes within a given gene." Applicants claim polynucleotides comprising a naturally occurring polynucleotide sequence at least 90% identical to SEQ ID NO:101 and polynucleotides encoding a polypeptide comprising a naturally occurring amino acid sequence at least 90% identical to SEQ ID NO:22.

The Final Office Action questions the truth of Applicants' statement in the Response filed June 24, 2003 that "one of ordinary skill in the art would recognize naturally-occurring variants of SEQ ID NO:3 having 90% sequence identity to SEQ ID NO:22" (Final Office Action, page 21). The Final Office Action alleges that "[o]ne could certainly determine whether a protein that one had obtained from nature were 90% identical to SEQ ID NO:22, but that same person, handed a protein in a test tube, would have no way of determining whether that protein were 'naturally occurring.' The same applies to the nucleic acid of SEQ ID NO:101" (Final Office Action, page 21).

Applicants note that sequence information is not provided in a vacuum. Identification of the source of the sequence will typically allow one to determine if it is naturally-occurring. Also, attempted deceit to hide the source will not preclude infringement.

Regarding the claimed sequences encoding biologically and immunologically active fragments of SEQ ID NO:22, the specification discloses a specific signature sequence, corresponding to a bromodomain, at residues A80-N140 (specification, page 79). The biological activities of bromodomain proteins as chromatin binding domains were well known in the art at the time of filing (see the Maruyama reference, page 6509, col. 1). Thus Applicants were clearly in possession of at least one biologically active fragment, explicitly identified in terms of its component amino acid sequence, at the time of filing. The Final Office Action asserts that the specification "only teaches general computer based methods to determine regions of high immunogenicity" (Final Office Action, page 22). On the contrary, selection of immunogenic epitopes, such as regions at the C-terminus or hydrophilic regions, is described in the specification at page 70, lines 2-7. One of skill in the art would clearly find it trivial to select the C-terminal fragment of SEQ ID NO:22. Selection of hydrophobic regions of SEQ ID NO:22 would also require minimal effort given the ready availability of programs to analyze the hydrophobicity of amino acid sequences. Thus the specification also provides an adequate written description of the recited polynucleotide sequences encoding biologically and immunologically

active fragments. An additional detailed listing of every possible such fragment is not required, and would only result in needlessly cluttering the specification.

Enablement rejections under 35 U.S.C. § 112, first paragraph:

The rejection of claims 23-29 under 35 U.S.C. § 112, first paragraph, for alleged lack of enablement was maintained. The Final Office Action asserts that depending upon the utility, the specification would be found to be enabling for SEQ ID NO:101 or polynucleotides encoding SEQ ID NO:22, and possibly methods of making the protein of SEQ ID NO:22, but not 90% variants or fragments (Final Office Action, page 27). For this reason Applicants respectfully submit that the rejection does not apply to claims 24, 25, and 29, which do not recite variants or fragments.

As discussed above regarding the utility rejection, in section F, the specification, along with what is well known in the art, teach that the claimed polynucleotides which comprise naturally occurring variants of SEQ ID NO:101 are useful in toxicology testing and expression profiling. As discussed above, because the claimed variants are naturally occurring, they are useful in toxicology testing and expression profiling whether or not they are able to hybridize to SEQ ID NO:101, since their own complementary RNA sequences are also found in cells.

The specification also discloses further ways to use the claimed polynucleotide variants. For example, variant sequences having at least 50% sequence identity to HTMPN-22 encoding sequences can be used as probes to detect related sequences (page 50, line 32 through page 51, line 1) including HTMPN-22 variants that may be associated with disease states, such as the diseases listed in the specification at page 36, lines 4-13). See the specification at, for example, pages 50-54 for disclosure of how to use the claimed sequences in diagnostic assays. SNPs may be used to identify particular human populations, or to identify propensities for disease states (page 23, lines 23-25). The variant polynucleotides could also be used in microarrays to identify genetic variants, mutations, and polymorphisms, and for disease diagnosis and development and testing of therapeutic agents (see the specification at, for example, page 55, lines 9-15). Thus one of ordinary skill in the art would know how to used the claimed variants without any undue experimentation.

Regarding the claimed biologically active fragments, the specification discloses a specific signature sequence, corresponding to a bromodomain, at residues A80-N140 (specification, page 79).

The Final Office Action is incorrect in stating that there is no activity ascribed to this fragment (Final Office Action, page 27) because the activities of bromodomain proteins were well known in the art at the time of filing. For example, a bromodomain has utility as a chromatin binding domain (see the French reference, page 1991, col. 1). It is known in the art that bromodomains can by themselves interact with acetylated histones, and thus serve as chromatin targeting modules, without requiring additional protein domains (see the Marayuma reference, page 6519, col. 1). Thus no additional experimentation is required to identify the chromatin-targeting region of HTMPN-22.

The Final Office Action also attempts to question whether the guidance provided in the specification is sufficient to allow one of skill in the art to make immunologically active fragments of SEQ ID NO:22. The selection of immunogenic epitopes, such as regions at the C-terminus or hydrophilic regions, is described in the specification at page 70, lines 2-7. Applicants respectfully direct the Examiner's attention to the enclosed Paul reference (Paul, W.E., Fundamental Immunology, Third Edition, Raven Press, New York, (1993), pages 249-251 (Reference No. 11, enclosed)), which demonstrates that the method disclosed in the specification has an extremely high likelihood of success. Paul concurs that "hydrophilicity has been proposed as a second indication of immunogenicity" and that of all 12 proteins tested, "**the most hydrophilic site of each protein was indeed one of the antigenic sites**" (Paul, page 249, col. 2 (emphasis added)). Thus the art confirms that based upon the guidance provided in the specification, one of ordinary skill in the art would be able to make and use immunogenic fragments of SEQ ID NO:22 (or polynucleotides encoding these fragments) without any undue experimentation.

Thus one of skill in the art would clearly understand how to use the claimed polynucleotides encoding biologically and immunologically active fragments.

As set forth in *In re Marzocchi*, 169 USPQ 367, 369 (CCPA 1971):

> The first paragraph of § 112 requires nothing more than objective enablement. How such a teaching is set forth, either by the use of illustrative examples or by broad terminology, is of no importance.
>
> As a matter of Patent Office practice, then, a specification disclosure which contains a teaching of the manner and process of making and using the invention in terms which correspond in scope to those used in describing and defining the subject matter sought

> to be patented *must* be taken as in compliance with the enabling requirement of the first paragraph of § 112 *unless* there is reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support.

Contrary to the standard set forth in *Marzocchi*, the Final Office Action has failed to provide any **reasons** why one would doubt that the guidance provided by the present Specification would enable one to make and use the recited polynucleotides. Hence, a *prima facie* case for non-enablement has not been established with respect to the recited polynucleotides.

For at least the above reasons, withdrawal of the enablement rejections under 35 U.S.C. § 112, first paragraph, is respectfully requested.

CONCLUSION

In light of the above amendments and remarks, Applicants submit that the present application is fully in condition for allowance, and request that the Examiner withdraw the outstanding objections/rejections. Early notice to that effect is earnestly solicited.

If the Examiner contemplates other action, or if a telephone conference would expedite allowance of the claims, Applicants invite the Examiner to contact the undersigned at the number listed below.

Applicants believe that no fee is due with this communication. However, if the USPTO determines that a fee is due, the Commissioner is hereby authorized to charge Deposit Account No. **09-0108.**

Respectfully submitted,

INCYTE CORPORATION

Date: February 3, 2004

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Attachments:

Declaration of John C. Rockett, Ph.D., under 37 C.F.R. § 1.132, with Exhibits A - Q;
Second Declaration of Tod Bedilion, Ph.D., under 37 C.F.R. § 1.132;
Declaration of Vishwanath R. Iyer, Ph.D., under 37 C.F.R. § 1.132 with Exhibits A - E; and
Ten (10) references published before the filing date of the instant application:
1) WO 95/21944, SmithKline Beecham, "Differentially expressed genes in healthy and diseased subjects" (Aug. 17, 1995)
2) WO 95/20681, Incyte Pharmaceuticals, "Comparative Gene Transcript Analysis" (Aug 3, 1995)

3) Schena et al., "Quantitative Monitoring of Gene Expression Patterns with a Complementary DNA Microarray," Science 270:467-470 (Oct 20, 1995)
4) WO 95/35505, Stanford University, "Method and apparatus for fabricating microarrays of biological samples" (Dec 28, 1995)
5) U.S. Pat. No. 5,569,588, Ashby et al., "Methods for Drug Screening" (Oct 29, 1996)
6) Heller al., "Discovery and analysis of inflammatory disease-related genes using cDNA microarrays," *PNAS* 94:2150 - 2155 (Mar 1997)
7) WO 97/13877, Lynx Therapeutics, "Measurement of Gene Expression Profiles in Toxicity Determinations" (April 17, 1997)
8) Acacia Biosciences Press Release (August 11, 1997)
9) Glaser, "Strategies for Target Validation Streamline Evaluation of Leads," Genetic Engineering News (Sept. 15, 1997)
10) DeRisi *et al.,* "Exploring the metabolic and genetic control of gene expression on a genomic scale," Science 278:680 - 686 (Oct 24, 1997)
11) Paul, W.E., Fundamental Immunology, Third Edition, Raven Press, New York, (1993), pages 249-251